

## REMARKS

With the cancellation of claims 7, 8, 19, 29, 31, 36-38 and 40-42, and the addition of claims 50-51, claims 1-6, 9-18, 20-28, 30, 32-35 and 39-52 are pending.

The amendments to claims 2 and 3 should not narrow the scope of the amended recitations because the amendments were done merely for grammatical purposes.

The amendments to claims 6 and 9, e.g. the replacement of “which does not substantially rearrange into another form” with “wherein no more than 15% of the torsemide modification II rearranges into another form”, are supported by the specification in page 5, lines 18-27. The replacement should not narrow the scope of the amended claim recitation because “substantial rearrangement” is defined in page 5, lines 18-20, of the specification to mean any rearrangement of more than about 15% of one polymorphic form into any other polymorphic form of torsemide, e.g. modification I.

The amendment to claim 11 is supported by the specification at page 5, lines 16-18, which discloses that “trace amounts” are about 0.5 to about 2 weight%. The amendments to claims 11, 18 and 28 are supported by the specification at page 8, lines 3-4, which gives about 40°C and 75% relative humidity as examples of “stress conditions”.

The new claims 50-51 are supported by page 8, line 25 to page 9, line 4 of the specification.

### Information Disclosure Statement

Applicants request that the Examiner return a copy of the PTO-1449 Form filed as a part of an IDS on May 28, 2002 with his initials to acknowledge consideration of the prior art references cited therein. A similar request was made in the Amendment filed on July 19, 2004. Applicants need the Examiner to return a copy of the PTO-1449 Form with his initials to make the record complete.

### Claim Objections

Claims 19 and 29 were objected to as failing to further limit claims 18 and 28, respectively. The cancellation of claims 19 and 29 has made the objection moot.

### Claim Rejections -- 35 USC 112

Applicants respectfully traverse the indefiniteness rejections of claims 6-15, 18-22 and 28-49 due to the recitations, “high purity”, “does not substantially change over time” and “stress conditions”. Applicants submit that one skilled in the art would understand the meanings of these recitations. However, to advance prosecution, these recitations have been replaced. Withdrawal of the indefiniteness rejections is requested.

### Double Patenting Rejections

Applicants respectfully traverse the rejection of claims 16-49 over the claims of U.S. Patent No. 6,482,417 (US ‘417) under the doctrine of obviousness-type double patenting. To advance prosecution, however, a terminal disclaimer over US ‘417 would be filed after the Examiner has held that at least some of the claims are allowable.

Applicants also respectfully traverse the double patenting rejection of claims 2-9, 11 and 13-15 under 35 USC 101 over claims 1-7 and 9-12 of US ‘417 because the inventions according to the instant claims 2-9, 11 and 13-15 are not same as the inventions of claims 1-7 and 9-12 of US ‘417. In the stable pharmaceutical formulation of claims 2-5, the formulation requires an excipient having a low moisture content, but claims 1-7 and 9-12 of US ‘417 do not require any excipient of low moisture content. The stable pharmaceutical formulations of claims 6-9, 11 and 13-15 do not require any pharmaceutically acceptable carrier, but the stable pharmaceutical formulations of claims 1-7 and 9-12 of US ‘417 require a pharmaceutically acceptable carrier. Thus, contrary to the Office Action, claims 2-9, 11 and 13-15 do not claim the same invention as claims 1-7 and 9-12 of US ‘417. Withdrawal of the rejection under 35 USC 101 is requested.

Furthermore, applicants respectfully traverse the obviousness-type double patenting rejection of claim 1 over claims 81, 82 and 85-87 of U.S. Patent No. 6,465,496 (US 496). The method of claim 1 starts with crude torsemide modification II in acetonitrile and water to form torsemide modification I, which is suspended in water and there are pH adjustments. In contrast, the method of claims 81 and 82 of US ‘496 start with suspending amorphous torsemide in water with no pH adjustments. Also, the method of claims 85-87 start with stirring amorphous torsemide in water with no pH adjustments. Applicants contend that these differences (e.g. related to the starting torsemide and pH adjustments) between the instant claim 1 and claims 81, 82 and 85-87 of US ‘496 would not have been obvious. Applicants also disagree that claim 1 is

encompassed by the claims of US '496. Withdrawal of the obviousness-type double patenting rejection of claim 1 is requested.

#### Claim Rejection -- 35 U.S.C. 102

Applicants respectfully traverse the anticipatory rejection of claims 1 and 6-49 over US '496. The Office Action relies upon Example 11 of US '496 in asserting the Example 11 discloses steps (a) and (b) of claim 1. Applicants respectfully disagree. Steps (a) and (b) of claim 1 requires adding crude torsemide modification II to a solvent comprising acetonitrile and water to form torsemide modification I. However, Example 11 discloses adding torsemide modification II in methanol, and stirring at reflux to obtain torsemide modification I. Therefore, Example 11 does not disclose steps (a) and (b) of claim 1. The Examiner might have confused Example 11 with Example 9.

The Office Action asserts that Example 12 of US '496 discloses steps (c), (d), (e), (f) and (g) of claim 1. Steps (c), (d), (e), (f) and (g) of claim 1 convert torsemide modification I formed in step (b) into torsemide modification II.

Even if Example 9 of US '496 were to disclose steps (a) and (b), and Example 12 of US '496 were to disclose steps (c), (d), (e), (f) and (g) of claim 1, applicants submit that US '496 does not anticipate the method of claim 1. This is because the aim of Example 9 was to convert torsemide modification II to torsemide modification I, but the aim of Example 12 was to convert torsemide modification I to torsemide modification II. US '496 does not disclose using the methods of Examples 9 and 12 sequentially. The two aims of Examples 9 and 12 are exactly opposite. To a person skilled in the art reading the disclosures of US '496, the methods of Examples 9 and 12 are independent. The person would not envision US '496 as disclosing combining the methods of Examples 9 and 12 because combining the methods of claims 9 and 12 would be akin to going through a circular route starting with the starting material, torsemide modification II, and ending with the same starting material, torsemide modification II. Because the starting material of Example 9 and the final product of Example 12 are both torsemide modification II, the person skilled in the art would understand US '496 as using the methods of Examples 9 and 12 as two independent and separate methods for preparing two different polymorphs of torsemide. US '496 does not disclose combining steps (a) and (b) with steps (c),

(d), (e), (f) and (g) of claim 1. Thus, in spite of Examples 9 and 12, US '496 does not anticipate claim 1.

Claims 6-49 were rejected as anticipated by US '496 because the Examiner took a position that the properties, e.g. stability, of torsemide modification II recited in claims 6-49 would be inherent to the product of the combined method of Examples 9 and 12 since the combined method of Examples 9 and 12 of US '496 is the same method used in the instant application in preparing high purity torsemide modification II. Applicants respectfully disagree. As discussed above, US '496 does not disclose or suggest combining the methods of Examples 9 and 12. The methods of Examples 9 and 12 of US '496 were taught by US '496 to be used independently. In contrast, the high purity torsemide modification II of the instant invention can be prepared by the novel combination of steps (a)-(b) with steps (c)-(g) of claim 1 (see page 11, line 25 to page 12, line 17, of the specification). Not preceded with steps (a)-(c), the method of Example 12 of US '496 would not necessarily result in high purity torsemide modification II. Therefore, the anticipatory rejection of claims 1-6, 9-11, 13-18, 20-28, 30, 32-35 and 39-52 over US '496 should be withdrawn.

Claim 12 is directed toward a stable pharmaceutical composition comprising torsemide modification II, wherein the torsemide modification II is not a high purity torsemide because the torsemide modification II contains about 0.5 to about 2% (w/w) of torsemide modification I. Applicants contend that US '496 does not teach torsemide modification II containing about 0.5 to about 2% (w/w) of torsemide modification I, or a method for making torsemide modification II containing about 0.5 to about 2% (w/w) of torsemide modification I. Thus, the anticipatory rejection of claim 12 over US '496 should also be withdrawn.

Applicants also respectfully traverse the anticipatory rejection of claims 6-9 and 11-15 over Dreckmann-Behrendt (US 5,914,336). The Examiner took a position that Example 5 of Dreckmann-Behrendt anticipates claims 6-9 and 11-15 because the oral tablet of Example 5 contains 10% torsemide modification II. Applicants note that the tablet of Example 5 also contains 45 wt% of each of torsemide modifications I and III. Thus, the torsemide modification II in the tablet of Example 5 of Dreckmann-Behrendt is not stable because the torsemide modification II in the tablet of Example 5 of Dreckmann-Behrendt is not high purity torsemide modification II (e.g. torsemide modification II containing less than 0.5% torsemide modification I) or torsemide modification II containing trace amounts of torsemide modification I (wherein

“trace amounts” are about 0.5 to 1% (w/w). As a result, applicants request that the anticipatory rejection of claims 6-9 and 11-15 over Dreckmann-Behrendt should be withdrawn.

#### Claim Rejection – 35 U.S.C. 103

Applicants respectfully traverse the obviousness rejection of claims 2-5 over Dreckmann-Behrendt, by itself, or in view of Ortyl et al (US 5,738,872). The Office Action relies on the pharmaceutical composition in Example 5 of Dreckmann-Behrendt and the Office Action relies on Ortyl et al for the disclosure of pharmaceutically acceptable excipients. Applicants contend that the obviousness rejection should be withdrawn because neither Dreckmann-Behrendt nor Ortyl et al teaches or suggests including a pharmaceutically acceptable excipient in a stable pharmaceutical formulation comprising an effective amount of torsemide modification II, wherein the excipient has a low moisture content.

#### Conclusion

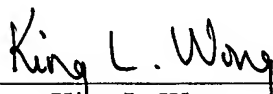
In view of the above reasoning, applicants submit that the application is in a condition for allowance. If anything can be done to expedite the prosecution, the Examiner is invited to call the undersigned to discuss it.

If the filing of this paper is deemed not timely, applicants petition for an appropriate extension of time. The petition fee, and any other fees that may be required in relation to this paper, can be charged to Deposit Account 11-0600, referencing Docket No. 01662/51303.

Respectfully submitted,  
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